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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,559	10/27/2003	Robert F. Kaiko	200.1102CON3	2420

7590 03/29/2005

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EXAMINER	
TRAN, SUSAN T	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,559	KAIKO ET AL.	
	Examiner	Art Unit	
	Susan T. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,8,10-20 and 36-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,8,10-20 and 36-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment, Request for Extension of Time, and Terminal Disclaimer filed 01/27/05.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. It appears that applicant's specification does not provide support for the following limitations:

"hydrocodone bitartrate" in claim 44;

"oxycodone hydrochloride" in claim 45;

"codeine phosphate" in claim 46;

"levorphanol tartrate" in claim 48;

"meperidine hydrochloride" in claim 49;

methadone hydrochloride" in claim 50; and

"morphine sulfate" in claim 51.

In accordance with MPEP § 714.02, applicant should specifically point out support for any amendment made to the disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5, 8, 12-14, 16-20, 44-47, 49-52 and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek US 4,769,372, in view of Dr. Medzon (Clinical Toxicology Review).

Kreek teaches an oral composition comprising combination of opioid analgesic and opioid antagonist (abstract, and column 5, lines 38-46). The opioid analgesics include hydrocodone, oxycodone, codeine, hydromorphone, meperidine, methadone, and morphine. Opioid analgesic is administered from 1 to 5 times daily in an amount of from about 1.5 to about 100 mg (column 3, lines 10-60; and column 4, lines 63 through

column 5, lines 1-15). Suitable opioid antagonists include naloxone, naloxone glucuronide and nalmefene (column 3, lines 63 through column 4, lines 1-5; and column 4, lines 17-36). Opioid antagonist is administered in an amount of from about 1 to about 18 mg (column 5, lines 58 through column 6, lines 1-13). The weight ratio of opioid antagonist to opioid analgesic is at least 0.01:1, which would fall within the claimed ranges (calculated from 1 mg of opioid antagonist and 100 mg of opioid analgesic). Kreek also teaches the oral dosage is in table, capsule, caplets, syrup, powder, elixirs and the like, with the use of carriers, binders, excipients, lubricants, disintegration agents, and sweeteners (column 5, lines 45-50).

Kreek does not teach naltrexone as an opioid antagonist.

Dr. Medzon teaches the use of naltrexone and nalmefene in place of naloxone for opioid detoxification (page 1, paragraphs 1, 2 and 5). Naltrexone is used in an amount of 50-100 mg daily (page 1, 3rd paragraph). Thus, it would have been obvious for one of ordinary skill in the art to modify the oral composition of Kreek using naltrexone as a suitable opioid antagonist, because Dr. Medzon teaches naltrexone by virtue of its' structural similarities to naloxone, shares the same properties exhibits by naloxone (page 1, 5th paragraph), because Dr. Medzon teaches naltrexone exhibits longer active opioid antagonists (page 1, 1st paragraph), and because Dr. Medzon teaches naltrexone has a high range of safety (page 3, 2nd paragraph). The expected result would be a dosage form comprising combination of opioid agonists and naltrexone suitable for oral administer that exhibits a low level of toxicity, low incidence of undesirable side effects, and low incidence of opioid abuse.

Claims 7, 10, 11, 15, 48 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek US 4,769,372, in view of Dr. Medzon (Clinical Toxicology Review) and Mitch et al. US 5,998,434.

Kreek and Dr. Medzon are relied upon for the reasons stated above. The references are silent as to the teachings of the additional non-opioid drug, as well as the sustained release carrier. However, Mitch teaches oral dosage therapeutic combination of compounds to provide analgesic activity. The dosage form comprising combination of aspirin and codeine or other narcotic analgesics; combination of NSAID and muscarinic compound; or combination of one or more opioid compounds and selected muscarinic compound (column 1, lines 15-16; column 26, lines 65 through column 27, lines 1-22; column 28, lines 1-14; column 29, lines 13-24). Mitch also teaches opioid compounds include levorphanol (column 27, line 66). Mitch further teaches the oral dosage is in the form of tablet, capsule, sachet, or other container, with the use of conventional carrier, wetting agent, emulsifying agent, sweetening agent, and other additives to provide quick, sustained, or delayed release of the active ingredient (column 30, lines 38-64). Thus, it would have been obvious for one of ordinary skill in the art to modify the oral dosage form of Kreek using naltrexone of Dr. Medzon, in combination of other analgesic compounds in an oral dosage form in view of the teachings of Mitch, because Mitch teaches combination of analgesic compounds that is more effective to relieve pain with diminishing side effects and toxicity (column 1, lines 15-23), because Dr. Medzon teaches naltrexone exhibits longer active opioid

antagonists (page 1, 1st paragraph), because Dr. Medzon teaches naltrexone has a high range of safety (page 3, 2nd paragraph), and because Kreek teaches oral dosage form that exhibits low level of toxicity and low incidence of undesirable side effects. The expected results would be a dosage form comprising combination of opioid analgesics and opioid antagonist compounds suitable for oral administration that is effective to relieve pain with low level of toxicity and diminish side effects.

Claims 10 and 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek US 4,769,372, in view of Dr. Medzon (Clinical Toxicology Review) and FDA Consumer.

It is noted that the cited references do not teach the salt form of naltrexone, *e.g.*, naltrexone hydrochloride (HCl). However, it is well known in pharmaceutical art to use salt form of active compound. To be more significant, FDA Consumer is cited for the teaching of naltrexone HCl suitable for oral dosage form, *e.g.*, Revia® tablet (see abstract). Thus, it would have been obvious for one of ordinary skill in the art to modify the oral dosage form of Kreek using naltrexone and naltrexone HCl in view of the teachings of Dr. Medzon and FDA Consumer because Kreek teaches oral dosage form comprising combination of naloxone and opioid agonist that exhibits low level of toxicity and low incidence of undesirable side effects, because Dr. Medzon teaches naltrexone exhibits longer active opioid antagonists (page 1, 1st paragraph), because Dr. Medzon teaches naltrexone is approved by the FDA for use in alcohol detoxification (page 1, 2nd paragraph), and because FDA Consumer teaches the safety of using naltrexone HCl for treating alcoholism. The expected results would be a dosage form comprising

combination of opioid analgesics and opioid antagonist compounds suitable for oral administration that has no toxicity and side effects.

Response to Arguments

Applicant's arguments filed 01/27/05 have been fully considered but they are not persuasive.

Applicant argues that Kreek teaches opioid antagonist which is substantially devoid of systemic antagonist activity when administered orally, however, naltrexone is not an opioid antagonist substantially devoid of systemic antagonist activity when administered orally. Thus, there is no motivation to combine Kreek and Dr. Medzon reference. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Kreek teaches the use of naloxone, and Dr. Medzon is relied upon solely for the teaching that naltrexone can be used in place of naloxone (page 1, paragraphs 1, 2 and 5) because naltrexone by virtue of its' structural similarities to naloxone, shares the same properties exhibits by naloxone (page 1, 5th paragraph), because naltrexone exhibits longer active opioid

antagonists (page 1, 1st paragraph), and because naltrexone has a high range of safety (page 3, 2nd paragraph).

Applicant argues that neither FDA consumer reference nor Mitch cures the deficiencies of Kreek and Dr. Medzon references. In response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan T. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-R from 6:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page, can be reached at (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SUPERVISORY PATENT EXAMINER
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